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THE MEDICAL GLEE CLUB

By J. M. Finlay

The reinstatement of "Daffydil" as an extra-curricular activity for medical students last year, under the most capable chairmanship of John E. McBirnie, brought with it not oratorical obscenity, but a host of those factors directly related to the nurturing and the longevity of good close student fellowship.

Reacting to its stimulus, the medical student body became prolific, and many of its talented members enlisted to add their weight to ensure the success of the production. New script writers, producers, stage managers, actors, actresses, dancers, musicians and vocalists were born, and became part of the family.

It was from this beginning that the Medical Glee Club evolved, and it is the purpose of this article to trace its evolution up to the present, to state its aims, and to give some proposals as to its expected future.

From a modest mid-summer dream of a ten-man chorus, there appeared on Sept. 20, 1945, some 40 to 50 male and female enthusiasts to attend the first meeting of the first recognized Medical Students' Glee Club. This number was later reduced to 30, including two most willing and extremely capable pianists, Ross Fleming and David Milrod. From a most insecure foundation in the beginning,

due to a lack of experience,—these individuals gave up their time to work together in a common interest, using any establishment available for practices (from fraternity houses to the Anatomy Building lecture room), to end up within a short two months by developing themselves into a choral group worthy of praise. These are the people to whom the present Glee Club truly owes its debt,—were it not for their combined efforts, and the final successful presentation of their work for "Daffydil", the Medical Music Association would not now exist.

Following close upon this début, the Glee Club was asked to present a Christmas programme for the Medical Arts and Letters Club. This conformed with the plan devised by Chairman John H. Crookston,—to use student talent for the Club meetings. Within three weeks the Glee Club had prepared and presented a one-hour programme of Christmas music, which embodied the spirit of the season, and which was made more enjoyable for all, by having the audience sing, as well. The Christmas season and with it the year 1945, was rounded off by a programme of carols given at the Hospital for Sick Children, and one evening, by a trip to various staff members' homes, for the purpose of carolling beneath their windows.

In the spring of 1946, many enthusiastic reports of the Glee Club, had been received, and worthy of note, a number of Staff members were among those who expressed this satisfaction. Dr. H. B. VanWyck, in particular, contributed much of this praise,—and built up morale, to the heights, when he expressed desire to become a member. The result of all this was the organization of a new and larger Glee Club, at present numbering 60 members and including the great majority of the original 30, plus Dr. VanWyck as Basso Profundo.

The Medical Society, which has supported all new and promising student activities, showed its interest by donating a worthy annual grant to what will be known at The Medical Music Association. As well, the Chairman of this newly-founded Association has been made a permanent member of the Medical Society, with the privilege of attending all regular meetings. The Music Association itself, now has its own executive of four offices.

All this preceding information is but a short and very sketchy history of what a group of medical students accomplished in six months. Of real import is the fact that this group of individuals is made up of students from all years in Medicine, of internes, and now, as well, a member of the staff. In such a group as this there quickly springs up real friendship independent of year level, or degree obtained. It has as its foundation, the joy of singing, and as such, it has provided a constructive outlet, which has certainly yielded a worthwhile reward. To ensure its survival, a rough outline of the aims of the Music Association are presented below:

1. To promote interest and participation in music, in the Medical Student body.
2. To bring to light, undiscovered musical talent in the student body.
3. To stimulate staff-student relationship, in a common interest.
4. To present, once yearly, an all-musical programme for medical students and staff, by Medical students and staff.

As a member of the student body, each one of us has a right to voice his ideas and opinions. Utilize this right, and if you have a suggestion which you would like to see fulfilled by the Music Association, jot it down, slip it in an envelope marked "Music Association" and leave it under the door of room 107, Anatomy Building. It will be happily accepted, and will receive the closest attention.

JOURNAL REVIEW

JOURNAL OF THE HISTORY OF MEDICINE AND ALLIED SCIENCES. Published quarterly by Henry Schuman, 20 E. 70th Street, New York 21, N.Y. Subscription rate in Canada and U.S.A. $7.50. Single copies $2.50.

The first issue of this Journal appeared in January 1946. It is devoted to the publication of work relating to all aspects of the history of medicine, public health, dentistry, nursing, pharmacy, veterinary science and the various sciences that impinge on medicine.

At present, the only other publication of this type is the Bulletin of the History of Medicine, edited by Dr. Henry E. Sigerist. It is the purpose of the Editor, George Rosen, to supplement this Bulletin, rather than compete with it.

This Journal should serve to revive the interest of medical men in the history of the profession, and in this way give further insight into the social and scientific aspects of the medical problems of our day.

THE APPLICATION OF THE PRINCIPLES OF MILITARY SURGERY TO CIVILIAN PRACTICE

F. G. KERGIN

The features of war wounds which render them particularily liable to infection are severe tissue damage, gross contamination, severity and multiplicity, resulting in depression of the vital functions of the patient and delay in reaching adequate treatment. In spite of these difficulties, in the recent war the treatment of wounds reached such a pitch of excellence that, toward the end of the campaign in North West Europe, 90-95 p.c. of all wounds in casualties who survived to reach the General Hospitals showed sound healing of the skin within three weeks of the time of wounding. Because medical memory is short and because a certain proportion of the wounds encountered in civilian practice exhibit some of the factors mentioned above which predispose toward infection, it is appropriate at this time to briefly record the method of treatment which was so successful in obviating infection in war wounds and to enquire into the indications for the application of the method to civilian practice.

The main principles of treatment are:—

1. Primary incision of the wound, with excision of devitalized tissue and drainage.
2. The protection of the wound from secondary infection and trauma by an occlusive dressing, usually plaster of Paris.
3. The closure of the wound by suture in 4 to 7 days.

These three principles in treatment are amplified below.

Primary Surgical Treatment—The object of this stage of treatment is to provide a sufficient incision to decompress the wound so that the exudate which accumulates in the damaged area, as the result of injury, may flow out of the wound instead of accumulating in the tissues and so raising tension and impairing circulation. The incision permits the surgeon to do the other things which are important as primary surgical treatment, to excise severely damaged tissue which is the culture medium which allows organisms, particularly anaerobes, to gain their foothold and to remove large foreign bodies and the cloth which they may have carried into the wound. The incision should be in the long axis of the limb and should be of sufficient length to accomplish both of the above purposes with safety. There is no attempt at a block excision of the wound, and no tissue is sacrificed which is viable. Above all, skin must not be wasted, only dead tags may be excised; the same prohibition applies to bone. Only small, completely detached chips may be discarded. In the course of the operation, the surgeon must constantly be alert to recognize and protect important nerves and vessels.

Having completed the wound toilet, the wound cavity is very lightly packed with plain, close-mesh gauze and, if the incision is larger than required for drainage, the skin may be partially closed by interrupted sutures. There must be no tension.

The Occlusive Dressing.—It has come to be recognized that the commonest and the most serious infections of wounds are due, not to the original contamination, but to contamination at a later stage, and that any wound which is dressed repeatedly will inevitably become infected. Every dressing means trauma to the delicate developing granulation tissue. Further, if it is possible to do so without too much trouble, someone is almost certain to disturb a dressing and look at the wound. The answer is to wrap the extremity in plaster, which securely protects the patient against change of dressing and, at the same time, has other important advantages. The plaster is carried beyond the joint above and the joint below the wound, so putting the damaged muscle at rest and allowing granulation tissue to develop, undisturbed by movement. The plaster attracts fluid and so assists in the drainage as attested by the slowly spreading stain on the surface of the splint. Proper splinting greatly decreases the discomfort of the wound and permits easy, comfortable transportation of the patient without shock. If there is a fracture, the plaster, with the addition of traction when necessary maintains reduction.

The plaster, which is applied using ordinary technique, should be lightly padded and split.

Wound Closure.—If primary wound closure is done, the exudate which accumulates increases the tension in the tissues, leading to oedema and impaired tissue nutrition, giving contaminating organisms an opportunity to multiply and invade. The result may be spreading infection or even septicemia. If closure is deferred until the exudative phase is over, oedema does not occur and contaminating organisms are confronted by tissue of high vitality which is further protected by a barrier of early granulation tissue. They are unable to invade, and either succumb or at the worst, cause only a local infection in the wound cavity.

The time for wound closure will be after the period of exudation and before the tissues have become fixed by granulation tissue. It will vary with the size of the wound and the degree of damage to the muscle. Superficial wounds should be closed in 3-4 days and deeper wounds in 6-7 days. The occlusive dressing is removed in the Operating Theatre and, if the wound appears clean, closure is carried out at once using all aseptic precautions. Usually the skin only is closed with interrupted sutures, but under no circumstances may dead space be left, and if necessary to achieve this end, a few sutures of catgut may be placed in the deep tissues. When closure is carried out within the period suggested, the tissues are not fixed and come together easily. No trimming or undercutting is required. Since the stage of reaction is over and swelling will not occur, a little tension is permissible. If muscle is involved, the support and immobilization provided by a plaster splint will allow the rest which is essential for healing.

Chemotherapy—The chemotherapeutic agents are bacteriostatic rather than bacteriocidal. They reinforce but do not replace the function of the tissues in destroying organisms. They can slow the progress of infection but if, due to a failure in treatment, the tissues are handicapped by the presence of dead tissue, or foreign material, or unrelieved oedema, serious infection will occur.

Before deciding when and how to use chemotherapy, one must consider which agent will be most effective. The organisms to be feared most are the Staphylicocci, Streptococci and Clostridia, and, against all these, the most effective agent known is penicillin. It is the drug of choice. In severely contaminated wounds, in which mixed infection may develop, there may be some virtue in using general administration of both penicillin and a sulphonamide, particularly as a prophylactic if primary surgery must be delayed. This was done with severe war wounds.

In the stage before primary surgery, which may be long under battle conditions, but should never be long in civilian cases, there is no virtue in applying any drug locally to a contaminated wound, but general administration of penicillin or sulphonamide or both, has some ability to limit and slow the progress of developing infection.

After the primary operation, if it is properly done, the patient is safe from the danger of spreading infection without chemotherapeutic help, and if the operation is incomplete, chemotherapy may not save him from infection. However, penicillin should be given for two reasons—first, it may, on occasion, compensate to some degree for a surgical error, and second, and more important, in combination with good surgery it will assist in destroying any remaining organisms in the wound and tend to create a wound which is sterile for secondary suture. At this stage the administration should be general, rather than local.

At secondary suture, the situation has changed. The reaction in the wound is no longer exudative, and local absorption is active. For the more superficial wounds, a local application of sulphanilamide or calcium penicillin is sufficient (or no chemotherapy at all, if the wound looks perfectly clean). For the deeper wounds involving muscle, and for compound fractures, general penicillin therapy should be used for five days after suture.

Indications.—The above is the plan of treatment which was so successful in the treatment of war wounds. What are the indications and contraindications for its use in civil practice? For wounds and compound fractures which are seen within 6-8 hours, in which there is little contamination and in which tissue damage is slight, careful wound toilet and primary suture, supplemented by penicillin therapy, will remain the treatment of choice. For those more serious injuries which may be seen later, which may have gross visible contamination, or great damage to tissue, or in cases in which the circulation to the extremity is impaired or questionable, treatment along the above lines will give protection to the patient, peace of mind to the surgeon and may avert tragedy. When in doubt, two-stage treatment should be used. Leaving a wound open under plaster never causes infection; if it is sutured within 7 days it will heal as well as if closed by primary suture, and the second operation is a small price to pay for the insurance against dangerous infection.

ANTIBIOTICS

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Antimicrobial agents are either of chemical or biological origin. The former consists of inorganic and organic compounds (such as the heavy metals, halogens, phenols, arsenicals, sulphonamides, etc.) while the latter include a variety of products of higher plants and microorganisms. The term antibiotic is specifically applied to crystalline compounds of relatively low molecular weight which have a biological origin. They should be clearly distinguished from antibodies. The latter although of biological origin are usually colloidal substances of high molecular weight which exert their effect through specific immunological reactions.

Since the demonstration in 1940 of the chemotherapeutic properties of penicillin, by Florey and his colleagues at Oxford, a tremendous amount of work has been done on antibiotic agents. How extensive this research has been will be appreciated by the fact that a recent book on the subject listed over a thousand references. Although most of the work has been done in the past few years it would be erroneous to think of this subject as one of recent origin. Actually it has been observed since the early days of bacteriology and was called Bacterial Antagonisms. For example, Pasteur noted that certain bacteria produced substances which affected the growth of other bacteria. Indeed in 1897 it was first reported that certain green moulds of the genus Penicillium repressed the growth of various bacteria; possibly that was the first observation on the effect of penicillin.

Florey's work, however, served as a tremendous stimulus to the search for antibiotic substances. It drove home the point that in bacteria, fungi and plants, there exists an unlimited number of very efficient synthetic chemists; chemists, furthermore, who do not have to be paid a salary. This stimulus to pursue the search for anbiotic substances really should not have been needed for Nature had long been demonstrating the phenomenon. From the higher plants had been obtained antimicrobial agents such as quinine from the bark of Peruvian evergreen trees, emetine from the dried roots of Brazilian shrubs and chaulmoogra oil from the seeds of trees in Southern Asia. Studies on the bacteriology of the soil repeatedly hinted that it is the natural medium for the development of bacterial antagonists. A simple experiment demonstrates this: if a micro-organism like Bacillus coli is added to sterilized soil it multiplies rapidly but when added to non-sterilized soil it dies out quickly. Either it is eliminated from the non-sterilized soil because it cannot compete with the soil population for food or because it is destroyed by bacteria present in the soil. The latter is the most likely explanation for as B. coli dies out in non-sterilized soil there is a marked increase in the total number of micro-organisms antagonistic to it.

The techniques which are utilized for the demonstration of antibiotic substances are so simple that almost anyone can do this type of research. One may either conduct indiscriminate tests with pure cultures of bacteria and moulds, or one may repeatedly add to soil various pathogenic bacteria, thereby enriching the soil with antagonistic organisms capable of destroying the bacteria added, or one may plant

soil samples on agar cultures of staphylococcus or B. coli and look for antagonism. By any of these methods it is possible to show that soils, composts and natural water basin contain an extensive population of micro-organisms possessing antibacterial and and antifungal properties. However, to discover which of these are true chemotherapeutic substances, requires a great deal of time and effort, coupled with a certain amount of good luck.

In the past few years thousands of cultures of bacteria and moulds have been tested. The surveys have even extended to the higher plants. In one study, for example, the extracts of 2300 species of flowering plants were tested against Staphylococcus aureus and Bacillus coli. No inhibitory power was found in drug plants such as the deadly nightshade or foxglove or in many plants recommended by the herbalists, but a good inhibitory effect was noted with extracts of buttercups, climbing shrubs, tulips and such festive things as cabbage, cauliflower, broccoli and onion.

The fungi in particular have been found to be prolific producers of antibiotic substances. In the genus Aspergillus 40 per cent of strains, in Penicillium 25 per cent and in Streptomyces (formerly known as actinomyces) 25 per cent produce substances which antagonize bacterial growth. Several strains produce more than one antibiotic substance; P. notatum, for example, produces penicillin and notatin while Aspergillus fumigatus makes at least four antibiotic substances. But the property of inhibiting the growth of bacteria is not characteristic of any one genus or even species; rather it is found to occur only in certain special strains within a given species.

More than fifty different antibiotics have been described and studied in considerable detail. It would seem unnecessary to discuss each of these in detail for very few of them can be utilized in the treatment of disease. Consequently only those that either illustrate a method for obtaining antagonistic organisms, or at one time were considered to have clinical possibilities and those of proven worth will be described.

The Pneumococcal Polysaccharidases were discovered by Dubos. He was looking for something to affect pneumococci and the method he used was very original. Pathogenic pneumococci are encapsulated. Without the capsular substance they are readily destroyed by the body and do not produce an infection. Dubos argued that if he could find something which would destroy the capsule then he might have a cure for pneumococcal infections. He realized that the search would be worse than looking for a needle in a haystack and that a special technique would be necessary to narrow it down to only the possible effective micro-organisms. He, therefore, devised a culture medium in which the sole source of carbon was the polysaccharide of the pneumococcal capsule so that only those organisms capable of breaking down the capsular substance would be able to grow on the medium. These culture plates he did not inoculate with ordinary every day garden soil but he travelled to swamps and swampy lands, for he reasoned that fermentations of all sorts must be taking place in such acid soils. Eventually from a cranberry swamp he found an organism which would grow on his culture plates.

The enzyme preparations made from this organism were quite effective in experimental infections in mice when injected simultaneously with the microbes into the peritoneal cavity, but were much less effective when injected at a site distant to the infected area. Some of the enzyme preparations were highly specific affecting, for example, only the capsule of pneumococcus type 3. Due to these two features they have no clinical application.

Tyrothricin, as first known as gramicidin, is made by B. brevis. It was also discovered by Dubos through repeatedly adding living staphylococcus to soil samples. Tyrothricin is haemolytic for red blood cells and consequently can only be used topically. Since penicillin affects the same micro-organisms and is non-toxic, very little tyrothricin is being used clinically now.

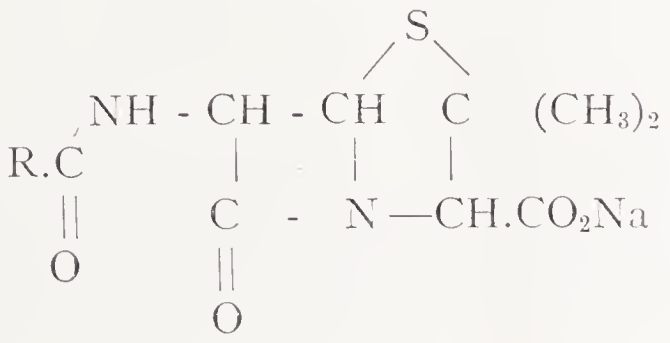
Penicillin is made by certain strains of Penicillium notatum and chrysogenum. Despite the great strides which have been made in its manufacture there is still a world shortage.

Four penicillins are recognized, called F, G. X and K. Penicillin made by surface cultures of the mould is mainly pencillin F and that made by submerged cultures Penicillin G.

Penicillin X differs in some of its physical characteristics from Penicillin F and G and recently evidence has been produced that organisms such as haemolytic streptococci, meningococci and gonococci are from two to eight times more sensitive to penicillin X than to G, while Streptococcus viridans, pneumococci and staphylococci are equally sensitive to each. Indeed, a strain of Strep. viridans from a patient with subacute bacterial endocarditis who had been treated with penicillin was found to be very resistant to penicillin G and quite sensitive to penicillin X. This patient was apparently successfully treated with penicillin X.

If substantiated this indicates a fundamental difference between the penicillins and also between penicillin and the sulphonamides. When an organism becomes resistant to one sulphonamide it is resistant to all .sulphonamide compounds. Apparently this may not be true from the penicillins but obviously more clinical material will have to studied before a reliable evaluation can be made.

The chemistry of the penicillins is now more or less known. All penicillins have the empirical formula $C_9H_{11}O_4SN_2.R$. In F-penicillin, R is Δ^2 pentenyl (i.e. $CH_3.CH_2=CH.CH_2$-); in G-penicillin, R is benzyl ($C_6H_5.CH_2$-); in X penicillin, R is p-hydroxybenzyl ($HO.C_6H_4.CH_2$-) and in K-penicillin it is n-heptyl (C_7H_{15}-). The constitution is not yet established unequivocally but the parent formula receiving most support is



The relationship between the dosage of penicillin used therapeutically, the resulting blood concentration and the in vitro sensitivity of bacteria to penicillin, is, by and large, not any too clearly understood. This is mainly due to the unitage value of penicillin. A unit of penicillin is defined as an amount which when diluted 1 in 50 completely prevents growth when an inoculum of standard culture of staphylococcus is added. In other words 1/50 of a unit inhibits staphylococci, or to use the decimal system .02 units. The dosage generally used in penicillin therapy is about 100,000 units per day. If given by continuous drip the blood concentration is approximately 0.1 units per c.c. of serum; with 200,000 units, 0.2. Standard therapy, therefore, attains a blood concentration which is perhaps five times the in vitro sensitivity of most susceptible organisms. However, fairly wide variations are encountered in the in vitro sensitivity of organisms belonging to the same bacterial species especially those isolated from cases of subacute bacterial endocarditis. Some strains may actually be resistant to as much as 5 units of penicillin per c.c. The proper treatment of this serious disease requires the laboratory determination of the sensitivity of the causative organism coupled with a total daily dosage of penicillin adjusted in accordance with the laboratory results.

In the treatment of infections caused by staphylococci, haemolytic streptococci, pneumococci, gonococci and other micro-organisms known to be sensitive to penicillin, the dosage should be doubled or trebled when the patient is not responding to routine therapy. At the same time the diagnosis should be questioned and a search undertaken for complications or associated diseases that might have an unfavourable effect on the patient's progress. Good results are obtained only when penicillin is brought in contact with the infecting micro-organism in the tissues and maintained at an adequate concentration for a sufficient period of time.

Actinomycin is produced by Streptomyces antibioticus. The early reports on actinomycin appeared promising for it is highly active against all species of bacteria tested as well as many fungi. Unfortunately it also is an extremely potent tissue poison.

Streptothricin, made by Streptomyces lavendulae, was at first thought to be comparatively non-toxic and possibly valuable because of its actions on gram negative bacilli and fungi. Chronic toxicity studies, however, revealed that it was toxic. It possibly may be used topically for the treatment of athlete's foot.

Clavicin, also known as patulin, is made by Aspergillus clavatus. Clavicin was thought to be of value as a topical treatment for colds but subsequent tests have failed to bear this out.

Streptomycin, which is made by Streptomyces griseus, has reached the stage of clinical investigation. It is particularly important because of activity against gram negative bacilli and the tubercle bacillus.

Crystalline streptomycin appears to be relatively non-toxic. On the other hand a product which has been only partially purified may contain a histamine-like impurity capable of producing fatal shock if a large dose is injected too rapidly into a vein. For systemic infections streptomycin is administered by continuous intra-

venous or intermittent intramuscular injection. The definition of the unit value of streptomycin is very different to that of pencillin. Depending on the infection to be treated the total daily dose of streptomycin administered generally varies between one and five million units. One million units per day given by continuous drip results in a blood concentration of about 10 units per c.c. of serum. Micro-organisms such as B. Coli, B. proteus, B. pyocyaneus, B. typhosus and Brucella tularensis are sensitive to streptomycin but the degree of sensitivity varies with each species and also between strains of the same species.

Clinical trials of streptimycin have given brilliant results in tularaemia. Good results in influenzal meningitis and in gram negative infections of the urinary tract have been obtained. The results in typhoid, paratyphoid and undulant fever have been poor. Streptomycin given by mouth is neither destroyed nor absorbed from the intestinal tract and consequently high concentrations can be obtained in the intestinal contents. This may be useful in the control of carriers of dysentry and cholera organisms.

The value of streptomycin in tuberculosis has not been determined fully but in experimental tuberculosis the results have been impressive. The first work was done by Feldman of the Mayo Clinic who has had a great deal of experience in the chemotherapy of experimental tuberculosis. In one experiment streptomycin therapy was commenced fifty days after the animals has been infected, when all were tuberculin positive, and was continued for 166 days. The guinea pigs were then killed. Autopsy reavealed that among the few surviving untreated controls tuberculosis was widespread while among the treated animals it was difficult to find any recognizable lesions. Of special interest was the observation that nine of 23 treated animals became tuberculin negative during treatment. At autopsy the spleens of these animals were injected into other guinea pigs and 7 of the 9 failed to produce disease. Feldman and his colleagues found streptomycin to be the most effective compound of any that they had tried in the treatment of experimental tuberculosis. It is worth remembering, however, that other substances such as promin and other sulphone compounds have given fairly dramatic results in experimental tuberculosis without showing the same promise in human tuberculosis. About all that can be said at the present time regarding the use of streptomycin in the treatment of human tuberculosis is that the response in early infiltrative lesions of the lung has been sufficiently encouraging to warrant an extension of the initial trial. Several cases of tuberculous meningitis have been treated with intramuscular and intrathecal streptomycin. These patients took a sudden and immediate turn for the worse and died within a matter of hours.

The most serious drawback to streptomycin is that bacteria quickly acquire resistance to it. In our hands four transfers of B. coli in streptomycin broth increased the resistance from 2 to over 1,000 units. We had the opportunity to treat a patient with subacute bacterial endocarditis with streptomycin. This case had previously been treated with penicillin and even though more than 1 million units a day had been given for three weeks, blood cultures had promptly become positive when therapy was stopped. The strain of streptococcus viridans isolated from

blood cultures was sensitive to 5 units of streptomycin per c.c. He was treated with one million units of streptomycin a day. During the first 24 hours blood cultures were negative and the streptomycin level in the blood was 12.5 units per c.c. The next day, however, the blood culture was positive, 1 colony per c.c., and the resistance of the culture had increased to 25 units per c.c. On the fourth day the blood was growing 72 colonies per c.c. and the culture resisted 500 units of streptomycin per c.c.—a hundred-fold increase in resistance in less than four days.

Present evidence suggests that the main usefulness of streptomycin, apart from tularaemia, will be in the treatment of gram negative infections, especially those of the urinary tract. Large doses will obviously have to be used to guard against acquired drug resistance. One is naturally very skeptical of its value in tuberculosis.

Bacitracin. The latest antibiotic is called bacitracin. This is a name without meaning unless one knows that it is a substance which is made by a bacillus cultured from the wound of a patient by the name of Tracy; hence bacitracin. It is a true chemotherapeutic substance for it is neutral, relatively non-toxic, diffusible, soluble in water and active in vivo when injected parenterally in the treatment of generalized experimental infections. It affects the same micro-organisms as respond to penicillin. Sufficient time has not yet elapsed to form any definite opinion as to the possible clinical value of bacitracin. However, it does possess the characteristics of a chemotherapeutic substance and as such merits full experimental and clinical investigation.

THE RELATIONSHIP BETWEEN THE TOXICITY, POTENCY, ACQUIRED SENSITIVITY AND THE CHEMICAL STRUCTURE OF SOME LOCAL ANAESTHETICS

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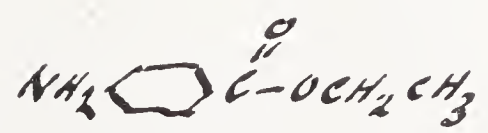
Procaine (trade name Novocaine), the first synthetic and still most widely used local anaesthetic, is by no means ideal. Because of its relatively low toxicity and sufficient potency for most purposes, it enjoys its popularity. However, it does not penetrate mucous membranes readily and has a short duration unless some vasoconstrictor is injected with it. For years chemists have sought to synthesize a product containing all the good qualities of procaine and possessing a greater potency, duration and penetrability. As a result, many new products have been prepared and described in the literature. Some of these with increased toxicity are also much more potent than procaine and may be used in more dilute solution. This overcomes the objection to the toxicity which is always associated with the concentration of the local anaesthetic. There appears a certain reluctance on the part of surgeons and dentists to use these less familiar agents in more dilute solutions.

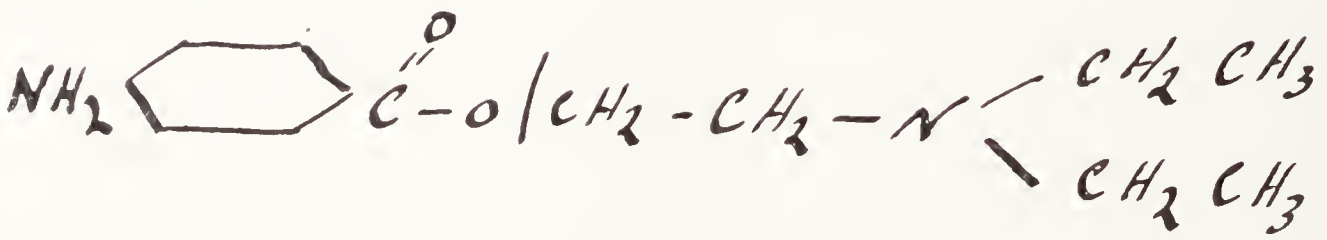
In the dental profession, a serious problem has arisen amongst dentists who use these local anaesthetics on patients and must work in the mouth without the protection of gloves. Some acquire a skin sensitivity to procaine so serious that they react when even dilute solutions of procaine touch their fingers. Patients in whom the drug is injected rarely exhibit this sensitivity. Unfortunately the practitioner sensitive to procaine shows a similar sensitivity to a number of other local anaesthetics. The cause of this sensitivity to some other anaesthetic solutions as well as the variations in potency and toxicity of some local anaesthetics, can be gained by a study of the chemical formulae of a few members of this synthetic group.

Most physicians, and quite a few students who have been away from organic chemistry for some years, find themselves bewildered when formidable chemical formulae are presented and hesitate to study them. A few minutes spent in becoming familiar with the formulae presented will bring a rich reward in a better understanding of potency, toxicity and why certain individuals sensitive to procaine are sensitive to various other local anaesthetics.

Most local anaesthetics contain three essential groups in their chemical structure. The first is an acid group containing the carboxyl group—COOH and a benzene or some other cyclic group. The most common acid group is NH_2 COOH, called para-amino-benzoic acid. The second is an ester group which may be looked upon as the alkyl group in an alcohol, i.e., everything in the alcohol but the (OH) group, for example $CH_3CH_2(OH)$ ethyl, CH_3CH_2 $CH_2(OH)$ propyl, etc. This alcohol links with the acid group to form an ester, the alkyl group replacing the hydrogen in the carboxyl group. The ethyl ester of the above acid would be  which could be called

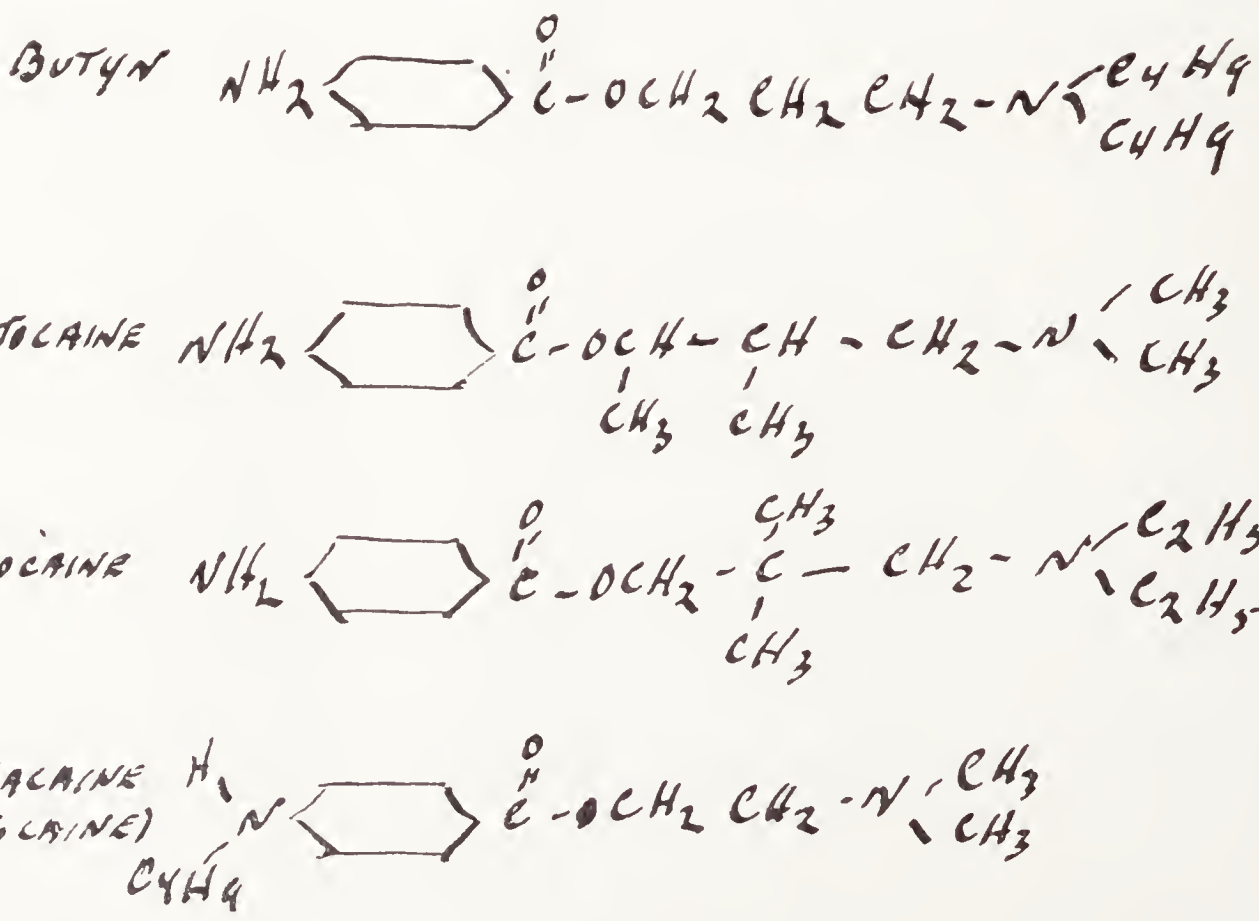
the para-amino-benzoyl ester of ethanol. This is benzocaine (trade name Anaesthesin) which is used in lozenges to relieve pain after tonsillectomy or after the extraction of teeth. It has a low toxicity and is only slightly soluble (1 in 2500). It does not penetrate readily and is unsuitable for surgical procedures.

Experimental chemical and pharmacological investigations soon indicated that linking a secondary or tertiary amine to the ester portion of benzocaine introduced many desirable properties. The potency was increased, it was sufficiently basic so that soluble salts could be made and its penetration was increased. Boiling in water did not decompose the product. The chemistry of this is very simple. The formula for ammonia is NH_3. In a secondary amine two hydrogens of ammonia are replaced by alkyl groups; a tertiary amine is ammonia with the three hydrogens replaced by alkyl groups. These groups may be similar or different. For example, if three ethyl groups were substituted we would have $CH_3CH_2\text{-}N\begin{matrix}\diagup CH_2CH_3\\ \diagdown CH_2CH_3\end{matrix}$. Ethyl alcohol will form an amine, amino ethanol $NH_2CH_2\text{-}CH_2OH$. The above tertiary amine formula closely resembles diethyl amino ethanol $\begin{matrix}CH_3—CH_2\\ CH_3—CH_2\end{matrix}\!\!\diagup\!\!\diagdown N CH_2CH_2OH$. If we were to link this alcohol with p-amino benzoic acid we obtain a product similar to that when benzocaine was formed, as indicated above,



This is para-amino-ester of diethylaminoethanol and is the familiar local anaesthetic, procaine. It consists of the acid group, an ester group and a tertiary amine group, the ester group being the alkyl linkage to the tertiary nitrogen.

The formulae of a number of related local anaesthetics are as follows:



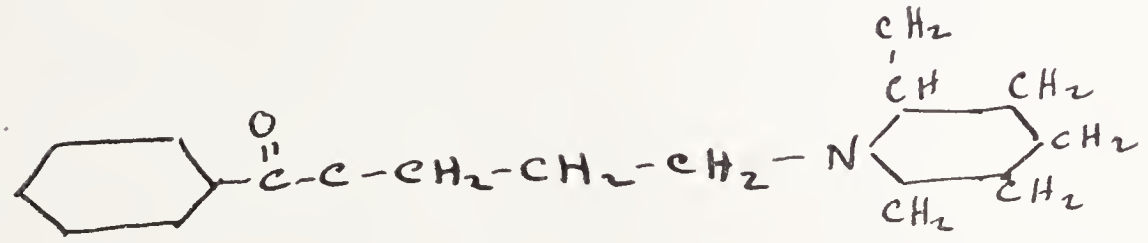
The striking similarity with these is that the acid group is the same in all. It is a para-amino benzoyl group (in Pontocaine is the N hydrogen substituted). It has been found that the individual sensitized to procaine is sensitive to all local anaesthetics having this particular acid group. Substitution of the hydrogen in the para amino group by alkyl groups, as in pontocaine, does not make any difference. If, however, the amino group is omitted, or is placed in some other position, i.e., ortho or meta, the individual is no longer sensitive to the anaesthetic.

It was mentioned before that the secondary or tertiary amino group made the anaesthetic basic so that it formed salts. The nitrogen in the basic group would add on HCl, thus $-CH_2CH_2N(C_2H_5)_2.HCl$, just as NH_3 and HCl form $NH_4Cl(NH_3.HCl)$, the nitrogen becoming pentavalent. It is believed that only the free base acts as an anaesthetic and that in the tissues the salt decomposes. Indeed, in a solution of sodium bicarbonate, procaine hydrochloride is much more effective than in saline. The disadvantage is that the procaine base is split off and becomes precipitated if the solution is allowed to stand a while.

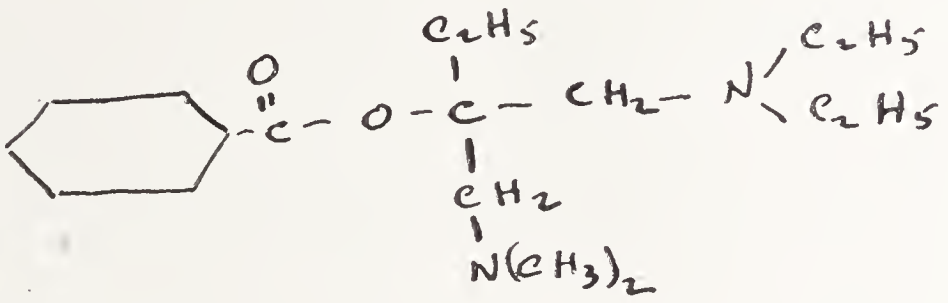
The aim of the chemist has been to keep the basicity as low as possible. This is done by making the ester group and the alkyl groups on the nitrogen as large as possible. Unfortunately when the ester group is increased the toxicity increases.

Below are given the formulae of three local anaesthetics which are on the market:

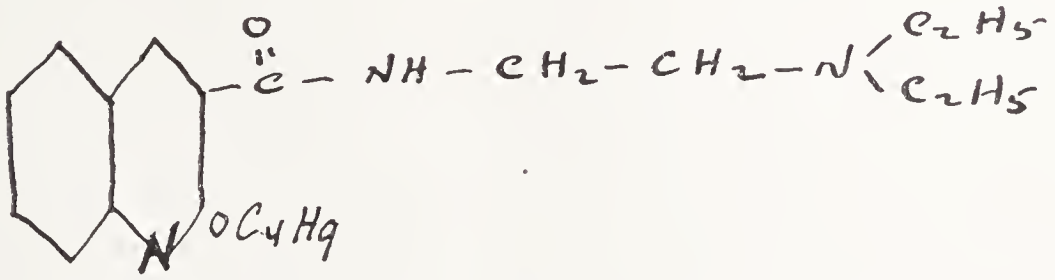
METYCAINE



ALYPIN



NUPERCAINE



This chemical information is of use to the surgeon or dentist. If one compares procaine and butyn, it is evident that butyn is more toxic than procaine and should be injected with caution and only in dilute solution. It should, and

does, penetrate readily and should be good for surface anaesthesia. If it came in contact with the skin of an individual sensitive to procaine it would cause a reaction. Both alypin and metycaine should have a high potency, toxicity and long duration but could be handled with impunity by the individual sensitive to procaine because there is no para NH_2 group. Nupercaine is in a class by itself. It is not a para-amino derivative and is not an ester, as is procaine. As its formula suggests the likelihood is that it would be very potent and possibly more toxic than the others. Persons sensitive to procaine could handle it without fear. Some of these local anaesthetics might be of greater value to the practitioner if he understood their chemistry.

LIVER FUNCTION TESTS—PART II.

By R. D. HAWKINS

C.—TESTS BASED ON THE ROLE OF THE LIVER IN INTERMEDIARY METABOLISM

a. *Protein Metabolism*

So far as tests of liver function calculated to test intermediary protein metabolism are concerned, little has been done which is clinically significant. One test, proposed by Mancke consists in the administration of 50 gm. of gelatin and the subsequent quantitative examination of the urine for amino acids. However, this test has not been shown to yield information of great practical value when performed on man.

Recently, Jankelson proposed the determination of free tyrosine in the blood filtrate as a liver function test to evaluate the state of this organ with respect to intermediate protein metabolism. Jankelson has studied the tyrosine content of fasting blood of normal individuals and of cases suffering from diseases of almost every system except the liver and has found that tyrosine could not be demonstrated in the fasting blood samples of such individuals. With the exception of cases of certain types of dermatitis, severe skin burns and possibly alkaptonuria, it would seem that the presence of free tyrosine in the blood filtrate can be referred to liver disease, but the absence of tyrosine does not exclude liver damage, since the incidence of positive results in focal injury of the liver is much smaller than in those where the injury is diffuse. The test may have prognostic significance, and Jankelson has suggested that by repeated tests some evidence as to the cause of jaundice may be obtained. The test is simple and accurate but minimal degrees of liver dysfunction cannot be determined by it. Perhaps a tyrosine clearance test, as Jankelson suggests, may enhance the sensitivity.

It can be said that, as yet, studies on protein metabolism cannot be utilized in the early diagnosis of liver dysfunction. However, this phase of hepatic physiology is still in its infancy and in time there may be evolved satisfactory methods for determining any alterations of this particular function.

b. *Carbohydrate Metabolism*

Galactose and fructose are the two sugars most extensively used as indicators in tests of liver function with respect to carbohydrate metabolism. However, it has only been within the last two decades that experimental evidence has accumulated which has revealed the reasons for their peculiar adaptability for this purpose. Glucose has occasionally been used to test hepatic function but the influence of factors other than the liver in the metabolism of this sugar renders it less satisfactory for this purpose.

The galactose tolerance test was originally introduced in 1906 and Shay and his co-workers were chiefly responsible for reviving an interest in it in this country. The test is based on the observation that a normal person can assimilate 40 grams of an oral dose of galactose without the loss of more than 2.5-3.0 grams of this sugar in the urine in the five hours immediately following the administration of the galactose. In the presence of hepatic injury conversion of this sugar into gylcogen fails sufficiently to allow a degree of glycosuria above this arbitrary level.

From the work of Shay, Schloss and Bell and Roe and Schwartzman it would appear that the oral galactose tolerance test may be employed in diabetics since according to these workers utilization of galactose by the liver seems independent

of the condition of the pancreas. Galactose is specifically utilized by the liver with practically none removed during the passage of this sugar through muscle tissue. Moreover, if any renal threshold exists for galactose, it must be extremely low. As advanced by Shay and Schloss, the chief field of usefulness of the galactose tolerance test has been in the differentiation of intra-hepatic jaundice from obstructive jaundice. These workers found that in all instances of catarrhal jaundice the urinary excretion of galactose exceeded 3.0 grams during the five-hour period, while the excretion in cases of obstructive jaundice did not exceed 2.2. grams. Actually, there are two serious stumbling blocks to the use of this test: the test is consistently negative in portal and biliary cirrhosis and is positive in from 25-40% of cases in which obstructive jaundice has persisted for a sufficiently long time to injure the hepatic parenchyma. In rather acute conditions associated with jaundice, a positive test is generally considered a strong argument for a primarily hepatic lesion, but in cases of chronic jaundice the results show a large margin of error and therefore it can probably be said that the oral test is not an infallibly reliable guide in differentiating obstructive jaundice from intra-hepatic jaundice. The duration of the jaundice interferes and the test is thus of questionable differential value after jaundice has persisted for two to five weeks. In addition, it must remembered that in cases where kidney damage is present, a false negative test may be obtained.

The sensitivity of the galactose tolerance test has been greatly increased and some of the disadvantages, such as the variations which can occur in intestinal absorption and renal excretion, have been overcome by an intravenous modification of the original oral test, the intravenous galactose clearance test.

In the intravenous modification proposed by Althausen and Stockholm, 1 c.c. of a 50% solution of galactose per kilogram of body weight is injected intravenously over a period of 4-5 minutes, after a control sample of blood has been previously removed. Test samples of blood are taken at 60 and 75 minutes, fasting blood being tested in all cases. Bassett, Althausen and Coltrin found that when 20 mg% plasma retention is taken as the dividing line, 90% of patients with hepatitis were above, and 83% of cases with obstruction were below this level, but these workers point out that confusion may occur if the obstructive jaundice has persisted for more than six months, or if the obstruction occurs in the presence of antecedent liver disease.

The evidence furnished by Bassett and his co-workers shows that the intravenous test is more sensitive than the oral test and can be used as a means of evaluating hepatic insufficiency and for prognosis. The extra work imposed upon the liver as required by the graded dose of the intravenous test seems worthwhile. However, the technique of the test is more or less involved, necessitating considerable detail in the analysis of the non-fermentable reducing substances in the blood. Moreover, as in the oral test, the duration of the jaundice must be considered in evaluating the results.

Cholesterol Metabolism

A study of cholesterol and cholesterol esters in the plasma in various types of disease of the liver has been carried out for many years. There is evidence that the liver possesses the power of storing cholesterol and that this organ plays a vital role in the esterification of cholesterol with fatty acids. The liver, therefore, appears to exert a major influence in the control of the blood level of cholesterol as well as in determining the proportion of the free to the esterified form.

There is general agreement that the total cholesterol in the plasma is elevated in obstructing jaundice. The hypercholesterolemia in such a condition has been found by some to result from an increase in the free cholesterol with a concomi-

tant rise in esterified cholesterol, while other investigators found that the increase is the result of increments in both free and combined cholesterol fractions. Jones has pointed out that the discordant results are due to attempts to compare results of analysis of whole blood, serum and plasma, use of methods of widely varying preciseness, failure to control the studies adequately, failure to realize the wide range of normal concentration of total cholesterol which renders interpretation difficult, failure to recognize the narrow range of variation of the normal ratio of free in total cholesterol, and failure to recognize the non-specific contribution of various physiological and pathological factors to the effect on the plasma cholesterol level.

The total plasma cholesterol remains normal or diminished in acute parenchymatous or degenerative liver disease. In one series of cases reported the total choltesterol was lower in the more severe cases and the depression was dependent upon the amount of hepatic damage. Persistently low ester levels have serious prognostic significance, whereas a rising ester level accompanies improvement. No alteration in the ester level may mean mild damage or may indicate that regeneration has occurred. In Laënnec's cirrhosis with jaundice, the free cholesterol and ester levels may be normal or somewhat lower. In Epstein's series, the majority of cases with cirrhosis without jaundice had normal cholesterol and slightly lower ester values. Complications, however, alter the above typical picture. Jones suggests that such factors as fever and failing nutrition play a part in producing noted changes and therefore great care must be exercised in the interpretation of results of the cholesterol determinations.

Greene and his associates concluded that the determination of blood cholesterol may be of great value in determining the prognosis of the surgical treatment of patients with disease of the biliary tract but that the reduction of blood cholesterol as seen more frequently in parenchymatous than in obstructive jaundice is of greater value as an indicator of the severity of the hepatic damage than as an aid in differential diagnosis.

It must be borne in mind, when one considers the use of the plasma cholesterol partition values as a routine laboratory method, that the technique involved in the estimation of free and total cholesterol requires considerable skill and care. Moreover, another limitation in the use of the information obtained from the cholesterol levels is that such levels are not a specific index of liver function: other conditions may be associated with changes in cholesterol metabolism, as diseases of the pancreas (diabetes mellitus,) of the kidney (acute glomerulonephritis and nephrosis), endocrine system (ovarian dysfunction, hypothyroidism and hyperthyroidism), infection, anaemia and numerous other conditions. In addition, the range of variations in the normal state and in diseases of the liver, thyroid and kidney overlap so much that results are, as a consequence, very difficult to interpret.

D. TESTS BASED ON THE EXCRETORY FUNCTION OF THE LIVER

Although a large number of dyes have been used to test the excretory function of the liver, only two, rose bengal and bromsulphthalein have come into common use, and the tests based on the excretion of one of these, *bromsulphthalein,* will be discussed here.

The Bromsulphthalein Clearance Test

In 1924 Rosenthal and White studied the physiological behaviour of various phthalein dyes. These dyes when introduced into the blood stream were removed by the liver and excreted into the bile. Bromsulphthalein was found to be the

most suitable for use as a test of liver function; it was non-toxic in the small doses adequate for such a test. In 1925 these same workers reported the results of the clinical application of the bromsulphthalein test for hepatic function and described their technique in detail. They advised the intravenous injection of 2 mg. of dye per kilogram body weight. From the vein of the opposite arm four cubic centimetres of blood were withdrawn after five minutes, thirty minutes and sixty minutes. The amount of dye remaining in the blood serum was estimated by colorimetric comparison with a set of colour standards in a block colorimeter. The main criterion for a positive test was the retention of any dye in the *thirty minute* specimen of blood serum.

Rosenthal's test has been in common use since 1925; when positive, this test affords reliable evidence of impaired liver function. The criticism of the test is that it does not detect frequently enough, impairment of slight or moderate degree. In other words, the test lacks sensitivity.

Reading the literature on the bromsulphthalein test one can experience a distinct sense of confusion, because of the many variations which have been made in the original method, both in the amount of the dye injected, the time intervals after which blood samples are withdrawn and the values which have been accepted as representing the normal.

In 1938 Macdonald, investigating the disappearance time of bromsulphthalein from the blood in normal cases, found that the general practice of considering thirty minutes as the normal clearance time constituted a period longer than his experiments indicated was actually the case, when two milligrams per kilogram were injected. He emphasized that an abnormal liver with its remaining reserve may perform the same amount of work as a normal liver if allowed sufficient time, and a normal organ should be able to perform a stipulated task more rapidly than an impaired one. He therefore reasoned that the rate of removal of the dye during the thirty-minute period should be determined by withdrawing blood frequently during this period and not only relying on a five-minute and a thirty-minute determination. In a later paper he suggested a further modification in his method: that a blood specimen be obtained every five minutes for 35 minutes, and that the amount of dye given be increased from 2 mg. to 5 mg. per Kg. body weight, the latter being the more ideal dose for testing hepatic reserve since it requires the performance of the maximum amount of work which the normal liver can do in a short time.

Mateer and his associates recommend that the older Rosenthal test be replaced by the serial method and in a later paper they demonstrated that the 5 mg. dose is more sensitive than the 2 mg. dose. Since sensitive tests are required in estimating hepatic reserve, because of the large factor of safety in the liver, the test employing the larger injection of dye is therefore more valuable. In this later paper, however, Mateer and his associates advise adopting as the standard, forty-five minutes as the normal disappearance time for the 5 mg. per Kg. dose.

On the other hand Israel and Reinhold advise that more than 60% of retention after 30 minutes be considered abnormal while Rosenberg and Soskin recommend variations between 0-10% in thirty minutes as within the normal range. However, as Matter has pointed out—"One patient may have 10% retention after 30 minutes and 0% after 45 minutes, whereas a second patient may have 10% after thirty minutes and 4-5% after 45 minutes. This prolonged delay in disappearance of the last small percentage from the blood is quite characteristic of impaired liver function and may be noted in many cases where the serial bromsulphthalein test is used. This fact has not been appreciated because the serial method is not generally employed."

When a decision has been reached as to the best means of evaluating the results and increasing the sensitivity of the bromsulphthalein test, a great deal of confusion will be removed from the literature.

In general it may be said of the bromsulphthalein clearance test that it is one of the most sensitive and reliable tests of hepatic insufficiency *in the absence of jaundice*. Invasion of the liver from abdominal and rectal malignant conditions has been detected by this test, and a relatively moderate hepatic involvement will produce a significant degree of dye retention in metastatic malignancy. The test is also of prognostic value—in the presence of a high grade retention the prognosis is so grave in malignancy that an operation is ordinarily of no value in increasing the longevity of the patient. Chapman and his co-workers have found that the average duration of life varied inversely with the degree of risk as indicated by this test. This information is of value to the surgeon in evaluating the risk in any contemplated surgical procedure.

So far as limitations of the original bromsulphthalein test and its modifications are concerned, the following may be said:

1. There is evidence which indicates that removal of bromsulphthalein from tthe blood stream is a function of the entire reticulo-endothelial system, of which the Kupfer cells of the liver are only a part.

2. The difficulty of determining accurately the degree of retention in highly icteric sera impairs the value of the test for comparative purposes; according to Snell and Magar, the bromsuphthalein test is not applicable or accurate in cases of clinical icterus.

3. Retention in extra-hepatic diseases is occasionally encountered; vascular stasis will produce a false positive result; the use of the test is also limited in the presence of lipemia and hemolysis.

E. MISCELLANEOUS LIVER FUNCTION TESTS

(a) *Measurement of Coagulation Factors*

It has been demonstrated that the liver is responsible for the formation of prothrombin and that the maintenance of the normal level of this substance in the plasma is governed by the presence of adequate vitamin K. A deficiency in plasma prothrombin is usually a result of either liver damage or of vitamin K deficiency, in the latter case generally because of a failure of intestinal absorption in biliary disorders. If vitamin K is provided in adequate amounts, therefore, the prothrombin level affords a measure of the function of the hepatic cells. For example, if in jaundice the prothrombin time is normal, then the margin of safety in liver function is relatively large; if the prothrombin time is prolonged but a response is obtained to parenteral vitamin K therapy, the prognosis and operative risk is good, but if no response or an inadequate response is obtained, the prognosis is grave.

Severe hepatic damage is usually associated with hypoprothrombinemia. When such a condition is due to extensive injury to the parenchymatous tissue of the liver, the administration of large amounts of vitamin K and bile salts has no effect on the prothrombin level of the blood even when it is available.

The prothrombin time not only gives an index of hepatic insufficiency but reveals a bleeding tendency as well. Patients with obstructive jaundice exhibit no tendency to haemorrhage as long as the prothrombin concentration remains above 50% of the normal, but when the prothrombin falls below 30-35% of the normal bleeding is likely to occur, chiefly from mucous membranes at operation, and from wounds, post-operatively. The determination of the prothrombin time thus affords information of great value in prognosis and in the estimation of the

surgical risk; it is also useful in determining the proper course of pre-operative and post-operative procedures. Frequent tests are indicated, for the prothrombin level can change rapidly, but all in all, the determination of the prothrombin level and the response of the patient to vitamin K therapy is one of the most practical tests of hepatic insufficiency. Various investigators have stressed the value of the prothrombin level and the response to vitamin K in the differential diagnosis of intrahepatic and extrahepatic jaundice. These workers found that the hypoprothrombinemia due to vitamin K deficiency secondary to obstruction of the common bile duct responded promptly and completely to the administration of the vitamin, whereas in cases in which the lowered prothrombin was due primarily to liver disease, vitamin K did not correct the hypoprothrombinemia. The ever-present difficulty that an uncomplicated case of obstructive or of non-obstructive jaundice is encountered infrequently makes the results of the plasma prothrombin response to vitamin K therapy as difficult to interpret as it does most other liver function tests recommended for such differential diagnosis.

Two limitations are evident in the determination of plasma prothrombin. The two stage techniques are more sensitive to hypoprothrombinemia and give more reliable prothrombin levels, but their technical difficulties preclude their general adoption as laboratory procedures for clinical diagnosis; on the other hand, the one-stage methods do not measure the quantity of prothrombin alone because they are an index of many variable factors, including the amount of prothrombin, the rate of conversion of prothrombin to thrombin, and the reaction of thrombin, the fibrinogen to form the fibrin clot. Although the one-stage technique does not accurately determine the level of prothrombin activity, it is nevertheless an excellent practical measure of the tendency to haemorrhage.

(b) *Serum Phosphatase*

Phosphatase is an enzyme which is found in high concentrations in bone, in the kidney and intestinal mucosa, in the liver and in the plasma. Its activity in the serum is measured as the difference between the serum inorganic phosphate after incubation of the serum with a suitable substrate, such as glycerophosphate or phenylphosphate.

There is evidence to show that various types of liver damage will produce an increase in the amount of phosphatase in the blood serum and these observations tend to indicate that the level of serum phosphatase activity may be a sensitive indicator of liver damage. Roberts first noted that high values for phosphatase in serum were a feature of some cases of obstructive jaundice, while in the non-obstructive types, normal or only slightly higher values were the rule. Roberts proposed the use of this test for differential diagnosis, but numerous subsequent papers in which attempts were made to differentiate between various types of jaundice have yielded conflicting results and one is left with no clear picture as to the merits of the test for differential diagnosis. There is little or no elevation of the serum phosphatase in hemolytic jaundice with is uncomplicated by liver obstruction or hepatitis.

The exact basis for the changes in serum phosphatase is still unsettled. Some workers have outlined a cycle of bone, to blood plasma, to liver, to bile, but according to Roberts, if obstructive jaundice results in a detouring of the bile to the blood, the concentration in the bile is not sufficient to account for the rise in the blood level of this enzyme. Moreover, although part of the serum phosphatase is osseous in origin, Bodansky and Jaffe have presented evidence that part of it is non-osseous as well. Somehow the facts or theories available do not seem to fit the results.

From a critical standpoint it may be said that the serum phosphatase level is a

sensitive test of liver damage, but it is not specific for hepatic disease. The level of the enzyme may be raised in diseases of the bone, such as osteitis deformans, or in hyperparathyroidism. In the differentiation between extrahepatic obstructive lesions and hepato-cellular jaundice, it would seem that there is sufficient overlapping in the elevation of serum phosphatase to make the test of doubtful value.

(c) *Cephalin-Cholesterol Flocculation Test*

In 1938 Hanger reported a simple test by which a disturbance in the liver parenchymal cells could be detected by noting the capacity of the blood serum of such patients to flocculate a colloidal suspension of a cephalin-cholesterol emulsion He stated that the positive reading should be made in terms of plus signs, a four plus reaction indicating a complete precipitation of the lipid emulsion with no remaining turbidity of the supermatant flued. He stated that he had found flocculation was consistently absent in all tests made on normal individuals but occurred in most instances where active disease of the liver parenchyma was present. Hanger maintains that all cases of catarrhal jaundice examined at the height of the attack gave a positive reaction which gradully became weaker and finally negative as clinical improvement took place. In cases of cirrhosis the degree of flocculation paralleled the severity of the process and was negative in those instances in which residual scarring was apparently the sole lesion. In cases of obstructive jaundice, except those of long standing, gave a negative reaction. In 1938 Hanger emphasized especially the value of this test in differentiating hepatogenous from obstructive jaundice and in following the course of hepatogenous jaundice. In the prognosis of acute hepatitis the progressive decrease and final disappearance of an orignal four plus test, before the jaundice had disappeared, indicated an excellent prognosis, but the continued persistence of a four plus test, irrespective of a decrease in the degree of jaundice, indicated progressive liver degeneration and often an unfavorable prognosis. Pohle and Stewart disagreed with Hanger on the suitability of the test for differential diagnosis, but the majority of the obstructive cases which they investigated were tested later in the course of the icterus than were those reported by Hanger.

The cephalin-cholesterol flocculation tests offer a very sensitive and reliable index of the activity of hepatic disease processes. Rosenberg and Soskin found that in 10% of cases of mild to moderate disease of the liver the test successfully disclosed clinically significant liver disease where all other tests and combinations of tests failed. They found a distinct correlation between the activity of the liver disease and the degree of flocculation obtained. Other tests of liver function were sometimes quite strongly positive in patients with mild or subclinical liver disease when the flocculation reactions were slight or negative. These workers interpret these results as instances of impaired liver function resulting from liver disease which is either slowly progressive or which has become quiescent.

There has been a good deal of discussion over the variations in the sensitivity of the cephalin preparations, depending upon slight modifications in the preparation procedure, and the age of the preparation. It is therefore necessary to run periodically, normal control sera to know how to interpret results.

As to the mechanism involved in the cephalin-cholesterol flocculation test, final information is not yet available. Cases with extensive disruption of nuclei seem to give the strongest reaction. Fatty degeneration, for example, usually fails to give the positive test. Hanger believes that the flocculation phenomenon is due to the gamma-globulin fraction of the serum. The albumin fraction from normal serum in suitable amounts can inhibit the flocculating action of gamma-globulin while an equal amount of the albumin fraction from cases of hepatitis cannot do so. A positive cephalin-cholesterol reaction may be observed when:

1. The gamma-globulin is abnormally high, as in Kala-Azar.
2. The albumin fraction is abnormally low.
3. The albumin fraction is so altered that it fails to inhibit the flocculation caused by the gamma-globulin fraction.

In cases of hepatitis the last-named condition is the most important phenomenon,, while in cirrhosis all three mechanisms probably play a role.

In summary it may be said that this test combines marked sensitivity with reliability, provided either ripened cephalin is used or else the false faintly positive reactions are regarded as negative; it is applicable to jaundiced and non-jaundiced cases; gradations in the readings afford a quantitative test as to the degree of liver impairment; the test involves the use of one of the simplest techniques employed in the evaluation of liver function; it has very good value in prognosis and is the best test, in the opinion of many workers for the detection and follow-up of the progress of the activity of the disease processes in liver disorders.

In the following table, the tests mentioned in this paper are regrouped from the standpoint of their particular usefulness in differential diagnosis and detection of hepatic insufficiency.

I Tests for Differential Diagnosis

1. Intravenous galactose clearance test
2. Urobilinogen determinations in urine and faeces
3. Duodeno-biliary drainage
4. Quantitative serum bilirubin
5. Cholesterol and cholesterol ester levels in plasma.

II Tests for Hepatic Insufficiency

1. Bromsulphthalein (5 mg. / Kg.) clearance test
2. Intravenous hippuric acid synthesis test
3. Serum phosphatase
4. Prothrombin level and response to Vitamin K. therapy.

III Tests for determining the *activity* of disease processes.

1. Cephalin-Cholesterol Flocculation test.

The most important of the problems confronting the clinician is that of differential diagnosis in liver patients, but it is in this particular field that available tests are least satisfactory. The more recent tests are much more sensitive in detecting liver damage than the older tests, but one seems to be confronted with the problem that if one wishes a test for differential diagnosis of extra-hepatic or intra-hepatic dysfunction, one must use a test which is not too sensitive. It does not seem possible to combine marked sensitivity with differential diagnostic ability. In consequence of this fact, it seems that the intravenous galactose clearance test, the urobilinogen determinations in urine and faeces, the results of duodeno-biliary drainage and possibly the quantitative serum bilirubin test and the level of cholesterol esters in the plasma are the most useful in the differential diagnosis of parenchymatous and obstructive jaundice.

The tests believed to be most useful in the detection of hepatic insufficiency from the standpoint of detecting the extent of liver damage and residual function and of following the course of liver disease, are the bromsulphthalein (5 mg/Kg) clearance test, the intravenous hippuric acid synthesis test and possibly the serum phosphatase test and the prothrombin level in response to vitamin K therapy. The bromsulphthalein test is of no great value in cases of marked jaundice, and the hippuric acid test in cases of kidney dysfunction, but aside from these drawbacks,

the two tests have been shown to be the most sensitive in the matter of detecting hepatic insufficiency.

In the detection and subsequent follow-up of the *activity* of the disease processes in liver dysfunction, the cephalin-cholesterol flocculation test seems the simplest and most sensitive.

In conclusion we may say that in the use of liver function tests one must always keep in mind that no one function can be depended upon to indicate the general status of the whole organ and that the reserve function of the liver is so great that functional abnormalities can be expected to appear only when most of the organ has been destroyed. Accordingly, for the estimation of hepatic insufficiency, the greater the sensitivity of the test, the earlier the insufficiency can be detected. In the case of differential diagnosis, however, since pure forms of intra-hepatic and extra-hepatic jaundice rarely exist, the less sensitive tests are of greater value.

The results of liver function tests should only be considered with relation to the impression gained from purely clinical study, for it must be remembered that the results of these tests at any one time are modified by the dynamic nature of the organ, by the kind of liver disease and its acute or chonic nature, by the degree of regeneration which may be superimposed on the destructive process and by the presence of infection.

Feature

C. L. ROGERS, Editor

COMBATIVE COCCI

Some skirmishing cocci, arranged in a chain,
  Were encamped on a broad intermuscular plane,
Engaged in a scheme, in discussion profound
  For making a raid on the tissues around.
But a wandering leucocyte, out as a spy,
  Caught sight of the camp and at once "did a guy"**
Through a withering volley of toxins that fell
  From a sentinel coccus that spotted the cell,
With movement amoeboid, astounding fleet
  He beat a most diapedetic retreat
To a telegraph office he noticed at hand
  And cabled the news to a neighbouring gland.
The cocci, on hearing the sentinel's news,
  Were already beginning to shake in their shoes.
But an officer shouted, "it's nothing to us;
  If the leucocytes come we will knock 'em to pus."
The phagocytes came with a rush from the gland,
  But the germs were intent upon making a stand.
And the general cried, "We will make 'em repent,
  Up cocci and at 'em," and at 'em they went.
The scene that ensued was a terrible sight
  The battle it raged for a day and a night
Till millions and millions of phagocytes slain
  Were heaped in an abscess that swelled on the plain.
The cocci were shouting and talking big talk,
  And crying, "We cocci are cocks of the walk,"
When their general suddenly cried through the strike,
  We're done for—I see the old Doc. with his knife."

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Abstracts

C. L. ASZKANAZY, Editor

CONTRIBUTORS

W. G. B. CASSELMAN

M. C. CORCORAN

R. G. MCCENDIE

MEDICINE I

THE EFFECT OF LOW AND HIGH CARBOHYDRATE MEALS ON THE BLOOD-SUGAR LEVEL AND ON WORK PERFORMANCE IN STRENUOUS EXERCISE OF SHORT DURATION. J. Haldi, J. W. Wynn. *Am. Journ. Physiol. 145*: 43. Jan. 1946.

Functional hypoglycaemia, which in its milder forms gives rise to weakness and fatigue, appears to be a well established clinical entity. In its treatment, good results have been obtained by restricting the carbohydrate intake and giving a high protein and fat diet. Some investigators have the theory that the intake of a large amount of sugar supplies an additional insulogenic stimulus which results in hyperinsulinism and hypoglycaemia.

The authors carried out a series of experiments on a number of normal healthy medical students with the following results:

(1) There was no appreciable difference in the blood-sugar level 3 hours after a low or high carbohydrate meal.

(2) There is no relationship between blood-sugar level and the sense of hunger and weakness.

(3) The amount of strenuous exercise that could be done, was the same after a high carbohydrate meal as after an isocaloric meal with a low carbohydrate percentage.

Therefore, the authors conclude that in normal healthy individuals a high carbohydrate diet is not conducive to hypoglycaemia and its usual symptoms, hunger, weakness, and fatigue several hours later; also that the hypoglycaemic syndrome which is relieved by restriction of the carbohydrate intake is a pathological condition and not a normal physiological response to a high carbohydrate meal.

R. G. MCC.

MEDICINE II

HYPERINSULINISM AS A FACTOR IN PEPTIC ULCER. E. M. Abramson: *Amer. J. Digestive Diseases 12,* 379-82 (1945).

Uniformly low late values of blood dextrose were obtained with dextrose tolerance tests administered to a group of patients with peptic ulcer. These results fulfilled Abramson's prediction that patients with peptic ulcer would have hyperinsulinism. His prediction was based on such observations as the rarity of peptic ulcers in diabetics, the production of symptoms of peptic ulcer by hyperinsulinism. and the possible relation of the production of the ulcers by the hyperperistalsis and spasm induced by hypoglycemia. The possibility that the hyperinsulinism, or at least the chronic hypoglycemia, is a factor in the etiology of peptic ulcer is suggested by the fact that patients with a clinical diagnosis of peptic ulcer but lacking X-ray confirmation of peptic ulcer have the same type of dextrose tolerance curves as those having X-ray confirmation. There was no control group.

W. G. B. C.

MEDICINE III

STREPTOMYCIN: ABSORPTION, DIFFUSION EXCRETION AND TOXICITY. Dorothy H. Heilman, F. R. Heilman, H. C. Hinshaw, D. R. Nichols, W. E. Herrell: *Amer. J. Med. Sci. 210,* 576. (1945).

A report of studies on streptomycin commenced at the Mayo Clinic in September 1944. The antibiotic was administered to human beings in amounts which theoretically could be considered to be therapeutically effective. Data for only 30 of the patients concerned in the study are tabulated. Streptomycin can be administered intravenously, intramuscularly, subcutaneously, by the intrathecal and oral routes, and by nebulization. It should be administered every 3 or 4 hours if intermittent methods of parenteral administration are to be employed. Unless large doses of streptomycin are given, diffusion into the cerebrospinal fluid does not occur readily. It is rapidly absorbed into the general circulation and is excreted mostly in the urine following parenteral administration. Streptomycin diffuses through the placenta and is available in the fetal circulation. It appears to be contrated and excreted also in the bile. The administration of fairly large doses of streptomycin in single or repeated injections was not accompanied by any serious or uncontrollable toxic reactions. No toxic reactions were evident after prolonged administration of streptomycin.

W. G. B. C

MEDICINE IV

STUDIES ON NEUROMUSCULAR DYSFUNCTION: IV. NEOSTIGMINE THERAPY OF ACUTE AND CHRONIC CERVICAL INTRAMUSCULAR FIBROSITIS. H. Kabat and C. W. Jones: *Arch. Physical Medicine 26,* 691- (1945).

Nine patients with acute cervical intramuscular fibrositis (stiff neck) were given rapid relief by the administration of neostigmine. In some cases one injection brought complete relief within twenty-four hours. One patient with chronic cervical intramuscular fibrositis of six years' duration was markedly improved by this treatment.

W. G. B. C.

MEDICINE V

ACCURACY OF HEMOGLOBIN DETERMINATIONS ON FINGER-TIP BLOOD. Dorothy G. Wiehl: *Milbank Memorial Fund Quarterly, 24,* 6-28. (1946).

Analysis of the sources of error and their magnitude for hemoglobin determinations made by the photoelectric method is presented. The difference between two samples of finger blood, the accidental error of one hemoglobin determination, the sources of accidental errors, and periodic variation in determinations are considered and the photoelectric method is compared with other methods.

From duplicate determinations on venous blood specimens from 200 subjects, the procedural error was estimated to be plus or minus 0.145 gm. of hemoglobin per 100ml. From 391 examinations where two independent determinations were made using blood of the right and left hand, the standard error on one determination was estimated to be plus or minus 0.174 gm. per 100 ml. Assuming the procedural error was the same in the two studies, the standard error for sampling variation was plus or minus 0.095 gm. for finger-tip blood. Right-hand samples, which were always taken first, were slightly but significantly higher than those for the left hand.

This difference could not be explained. Significant variations in average levels during serial examinations suggested technical variations due to different technicians.

W. G. B. C.

SURGERY I

C. F. List and F. J. Hodges "Intracranial Angiography; the Diagnosis of Vascular Lesions" *Journ. Neurosurgery* vol. 3 (1). Jan. 1946.

Cerebral angiography is used to determine site and nature of suspected vascular lesions, especially in patients requiring surgical treatment. The method is contra-indicated in cases of advanced arteriosclerosis, hypertension, cardiac decompensation, recent embolic or thrombotic episodes, mmost patients with acute intracranial haemorrhage and in very old people, since there is the potential hazard of increasing vascular damage by producing spasm, thrombosis, or even rupture of the vessel.

The authors describe the technique, with Therotrast as contrast medium. It is not possible to inject the entire intracranial vascular system by one single procedure. If both hemispheres are to be studied, bilateral injection is required. Carotid or vertebral injection must be used to demonstrate the respective arborizations of these vessels.

A series of 35 patients with intracranial vascular lesions is reviewed. The typical findings in cases of vascular occlusions and coarctations, intracranial aneurysms, arteriovenous fistula of the internal carotid artery and the cavernous sinus, and vascular malformations are described.

M. C. C.

UROLOGY I

R. A. Burhans "Treatment of Orchitis of Mumps" *Journ. Urology* 54: 547 Dec. 1945.

The orchitis of mumps is the result of the formation of an acute hydrocoele around the testis, which, in contradistinction to a slowly forming hydrocoele, causes strangulation, acute inflammatory oedema and ultimate fibrosis and atrophy of the testis.

If a small scrotal incision is made during acute orchitis, an acute hydrocoele is encountered. The fluid in the tunica vaginalis is under extreme pressure and has a viscid yellowish colour. If drainage is accomplished at this time, no further therapeutic measures are needed. The temperature curve then resembles that of a pneumonial crisis. If drainage is delayed until acute swelling and fever have developed, the acute tension and pressure of the hydrocoele are absent and the testis is of a blackish colour. On incision of the tunicae propria and albuginea, the testicular tissue presents an appearance of bulbous oedema and inflammation.

After following cases in naval personnel for several months, the author has come to the conclusion that in early cases incision and drainage of the acute hydro-

coele with removal of the drain in 48 hours is indicated. In late cases, incision of the tunica vaginalis and incision and drainage of the tunicae propria and albuginea should be employed.

M. C. C.

PSYCHIATRY I

A. Abrahams "Chronic Fatigue" Lancet 249:421. 1945.

Fatigue is not an outstanding symptom in most organic diseases except the most severe ones. When fatigue is the outstanding complaint of a patient, usually no physical cause of it can be discovered. Therapy of such a condition is difficult for a physician unfamiliar with psychosomatic medicine. Focal infections, autointoxication, especially from the intestinal tract, night starvation, and particularly avitaminosis have been exploited as causes of chronic fatigue. Consequently an immense amount of medication, from vitamins to sedatives and tonics, is given to the patient.

A psychosomatic consideration, on the other hand, associates chronic fatigue with the state of weakness and exhaustion in hypoglycaemia. This, in turn, is connected with the endocrines. The influence of psychological factors on the endocrine system and its consequence on fatigue could thus well be linked up. Thus the influence of irregular living is discussed as a factor in the aetiology of chronic fatigue. It is stated that fatigue rarely results from intellectual work which is enjoyed. "Complaint of overwork is an indication of mental ill health, not a cause. The doctor has to look into the personality to find out the part actually played by the physical and mental output in the production of chronic fatigue . . ."

W. G. B. C.

PUBLIC HEALTH I

Tuberculosis Control. G. C. Brink: *Can. J. Public Health 37*, 1-6. (1946).

A survey of certain aspects of the control of tuberculosis in Canada, today and in the future, which presents the following facts: Average death rate due to tuberculosis in Canada is 16 per day. During the past 10 years, approximately 60 per cent of all tuberculosis deaths and over 60 per cent of all patients entering sanitoria were in the most productive age group, 20-49 years. Average cost (including loss of wages, clinical and hospital care) when wage earner is incapacitated by tuberculosis has been estimated at $5,400.00 for male and $5,000.00 for female. Estimated (by Mothers' Allowance Commission of Ontario) cost to taxpayer for assistance to family because of tuberculosis is $2,800.00. In Ontario, seven times as much money is spent on treatment as on prevention. A future programme for the control and elimination of this preventable disease must include: adequate facilities for early diagnosis, adequate and prompt sanitorium treatment for every active case of tuberculosis, adequate public health nursing services, social services to increase standard of living in families represented by tuberculosis, rehabilitation of the handicapped patient.

W. G. B. C.

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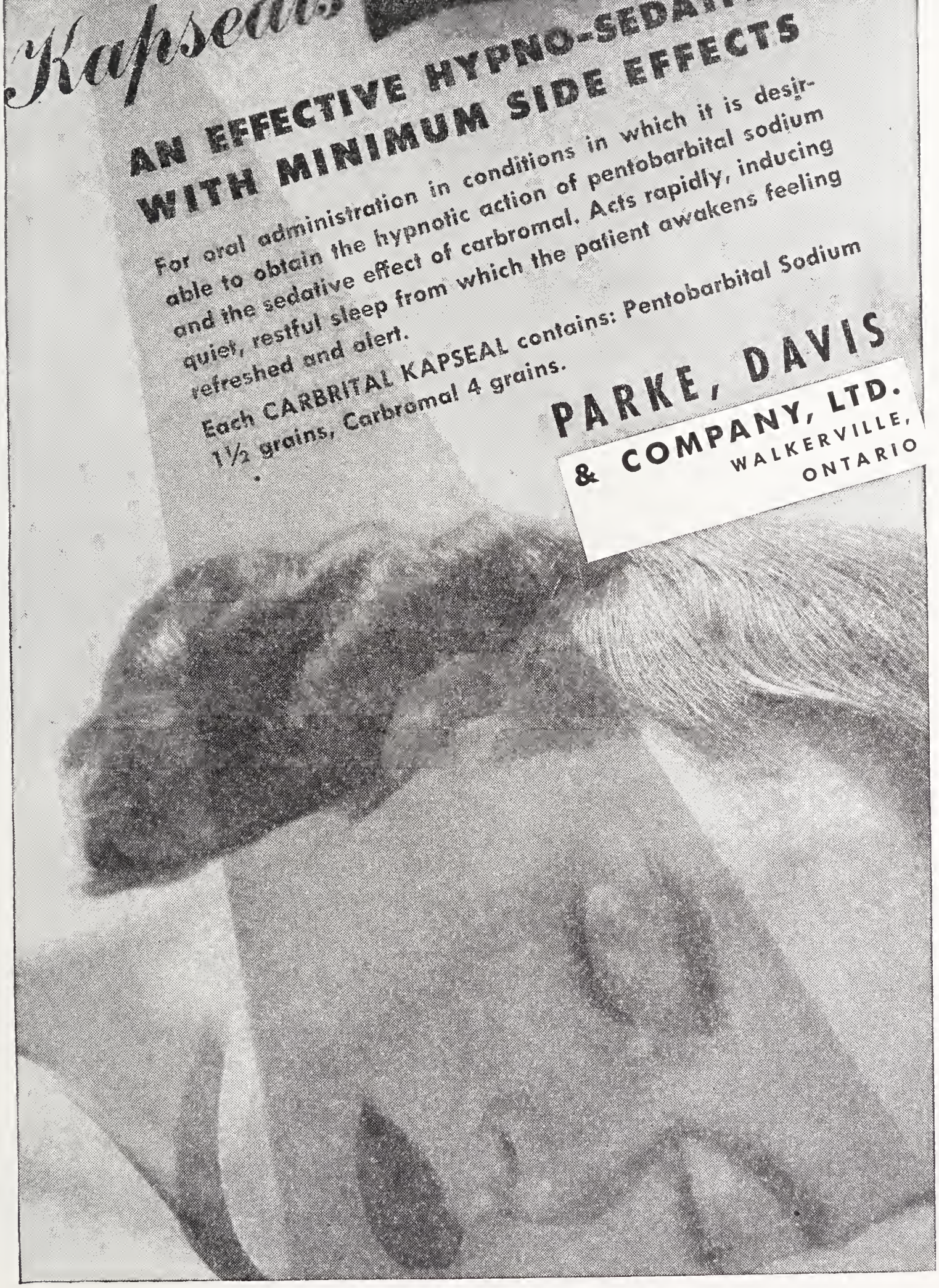

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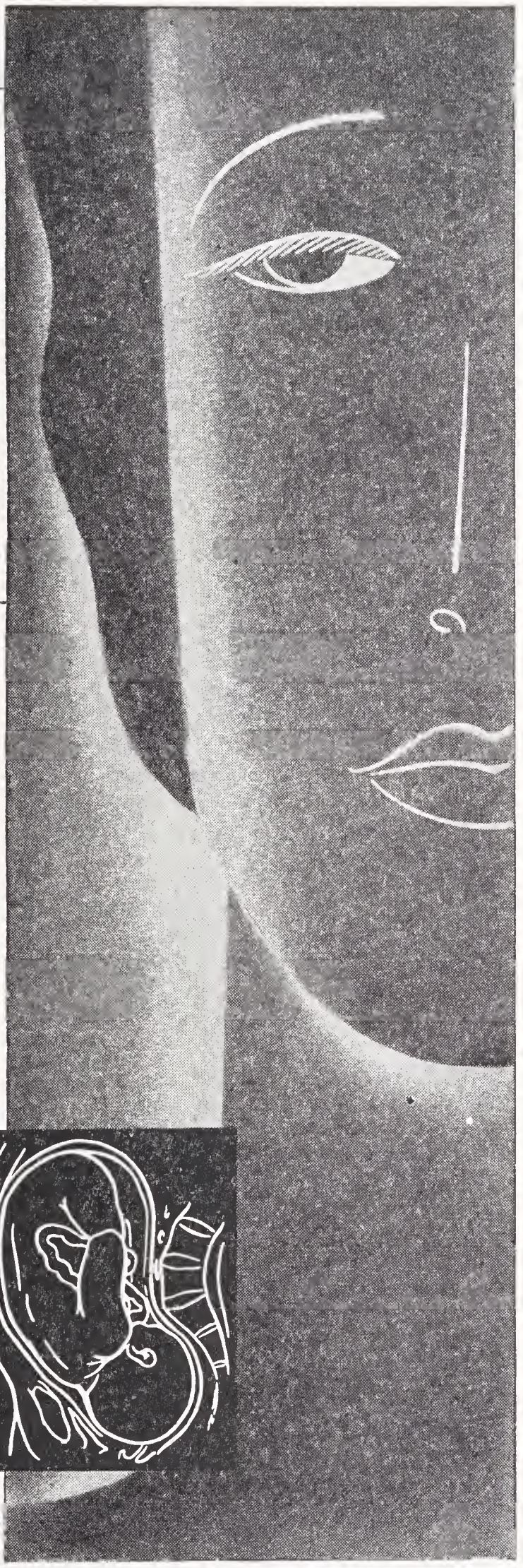

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1. LUND, CURTIS, J., KIMBLE, Marion S., Plasma Vitamin A and Carotene of the Newborn Infant, Am. J. Obs. & Gynec. 46:207:1943 (August).

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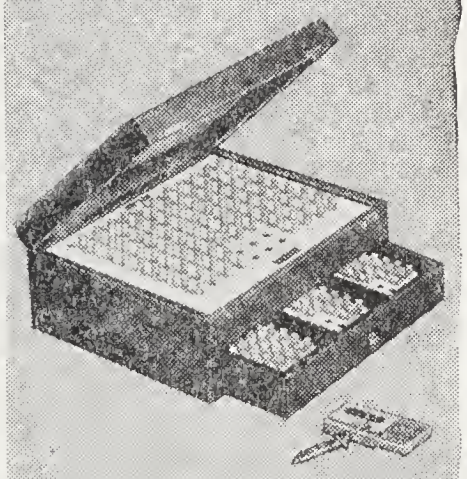
ALLERGY DIAGNOSIS



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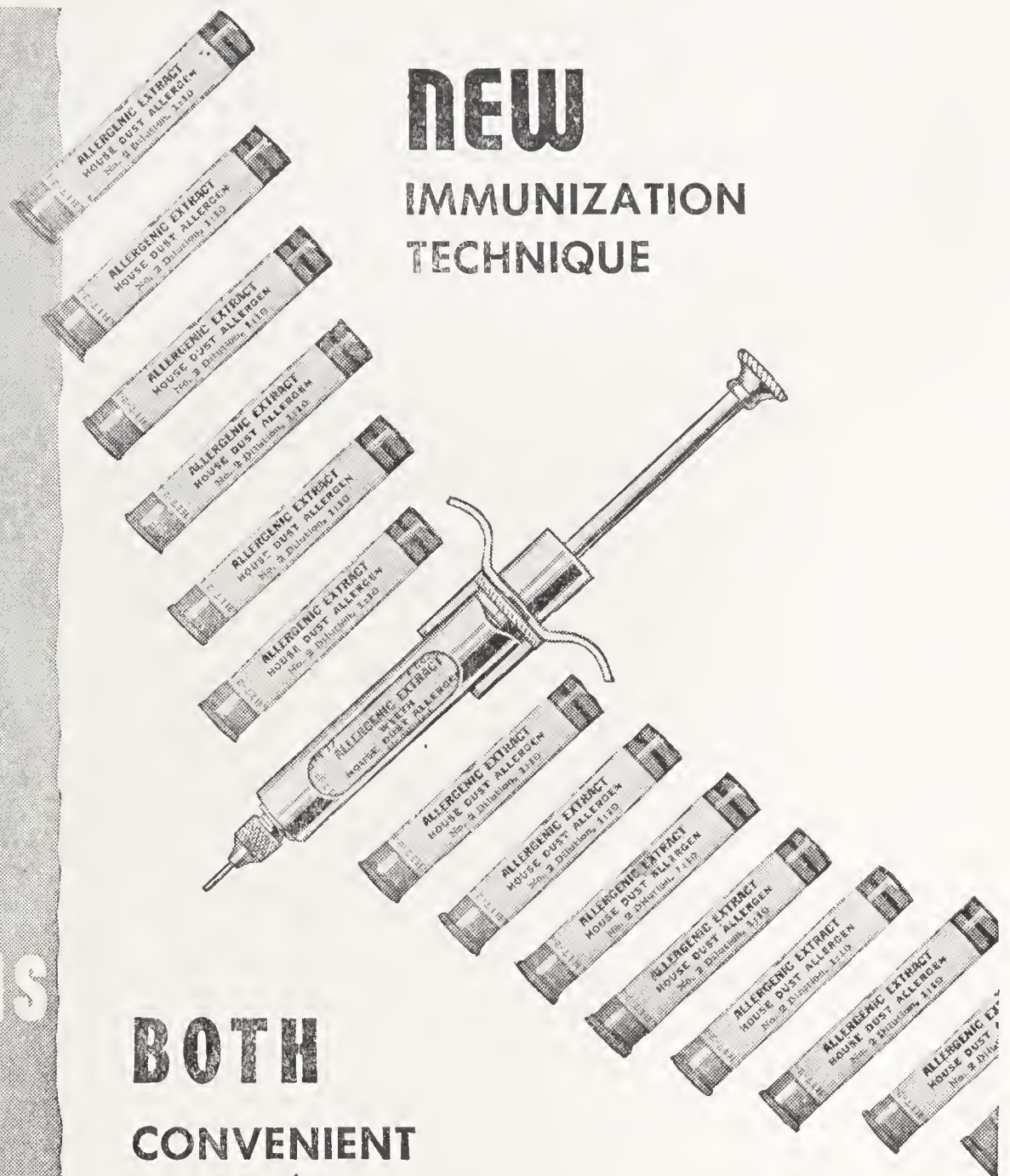

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